REMARKS

Enclosed is a copy of the NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES which was included with the July 2, 2001 Official Communication.

Status of the Claims

Claims 1-8 are now pending in the application. The specification and Claim 3 have been amended as described elsewhere herein. The amendments introduce no new matter. Support for the amendments is found throughout the specification and original claims.

The Application is in Compliance with the Sequence Listing Rules:

The Examiner states that the communication filed February 20, 2001 was not fully responsive to the office communication mailed January 17, 2001 because the specification and claims lacked sequence identity numbers. The specification has been amended to recite sequence identity numbers where appropriate.

The Examiner states that "no sequence identifiers have been provided for amino acid residues 144-314, 71-119, or 26-144" of human filaggrin. It is Applicants' belief that the Examiner intended to refer to amino acid residues 76-144 rather than 26-144. Applicants submit that the sequence of human filaggrin is known to those skilled in the art. The sequences identified by recitation of the amino acid boundaries of certain regions of the human filaggrin unit are also known to one of skill in the art. Therefore, it is unnecessary for Applicants to provide sequence identity numbers for the regions of human filaggrin identified by the indicated amino acid boundaries. Nonetheless, Applicants have provided a sequence identity number (SEQ ID NO:3) for amino acid residues 71-119 of human filaggrin. Further, Applicants have amended Claim 3 to recite SEQ ID NO:3 rather than amino acid residues 71-119 of human filaggrin.

Applicants submit that the amendments to the specification and claims bring the application into compliance with the sequence listing rules and respectfully request examination of the application.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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"Express Mail" Mailing Label Number Date of Deposit: I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Box Patent Application, Commissioner for Patents, Washington, DC 20231. _____	**CERTIFICATE OF MAILING** I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on. July 25, 2001 Lorna Morehead

Version With Markings to Show Changes Made:
In The Specification:

Please amend the paragraph on page 6, lines 8-13, as follows:

An antigen in accordance with the invention may for example consist of a peptide comprising all or part of the sequence corresponding to amino acids 71 to 119 (SEQ ID NO:3) of [or] a human filaggrin unit, in which at least one arginine residue has been replaced with a citrulline residue.

Please amend the paragraph on page 8, lines 32-38, as follows:

A DNA fragment encoding a filaggrin unit is amplified by PCR, using human genomic DNA (RAJI cells: ATCC CCL86) with the aid of the following 2 primers:

(SEQ ID NO:1) 5' primer:

5' TTCCTATACCAGGTGAGCACTCAT 3'

(SEQ ID NO:2) 3' primer:

5' AGACCCTGAACGTCCAGACCGTCCC 3'

Please amend the paragraph on page 12, lines 34-36, as follows:

EXAMPLE 4 : CITRULLINATION OF THE PEPTIDES S-47-S (SEQ ID NO:3) AND S-35-R (SEQ ID NO:4) BY PAD, AND TEST OF THE REACTIVITY OF THE CITRULLINATED PEPTIDES.

Please amend the paragraph on page 12, lines 37-39 and page 13, lines 1-12, as follows:

The peptide of 49 amino acids S-47-S (SEQ ID NO:3) having the sequence (1-letter code):

NH2-STGHSGSQHSHTTTQGRSDASRGSSGSRSTSRETRDQEQSGDGSRHSGS-COOH

corresponding to amino acids 71 to 119 of the sequence of a human filaggrin unit, and comprising 6 arginine residues, and

the peptide of 37 amino acids S-35-R (SEQ ID NO:4) having the sequence (1-letter

code):

NH2-SQDRDSQAQSEDSERRSASASRNHRGSAQEQSRDGSR-COOH

corresponding to amino acids 155 to 191 of the sequence of a human filaggrin unit, and comprising 7 arginine residues, were prepared by peptide synthesis. The peptides S-47-R and S-35-R are represented in the sequence listing in the annex under the respective numbers SEQ ID NO: 3 and SEQ ID NO: 4.

Please amend the paragraph on page 13, lines 13-20, as follows:

These 2 peptides, as well as fil-gst, were citrullinated by the action of PAD, for 30 minutes at 50°C, in the same reaction medium as that indicated in Example 2. The specific conditions for each peptide, and for the fil-gst are the following:

- peptide S-47-S (SEQ ID NO:3): 4 mU / μmol arginine
- peptide S-35-R (SEQ ID NO:4): 2.7 mU / μmol arginine
- fil-gst: as indicated in Example 2.

Please amend the paragraph on page 13, lines 34-38 and page 14, lines 1-6, as follows:

The results are illustrated by Figure 5, which shows that:

- AHF4 recognizes the peptide S-47-S (SEQ ID NO:3) and fil-gst, citrullinated or not, but does not recognize S-35-R (SEQ ID NO:4), citrullinated or not.

- S-47-S (SEQ ID NO:3) is recognized, after citrullination, by the serum from the patient suffering from RA, whereas S-35-R (SEQ ID NO:4), citrullinated or not, is not recognized. The same serum recognizes, moreover, the AVFs and the citrullinated fil-gst but does not recognize the noncitrullinated fil-gst.

Please amend the paragraph on page 14, lines 7-9, as follows:

EXAMPLE 5 : SYNTHESIS OF THE PEPTIDES E-12-H (SEQ ID NO:5) AND E-12-D (SEQ ID NO:6) CITRULLINATED AND NONCITRULLINATED AND TEST OF THE REACTIVITY OF THE PEPTIDES.

Please amend the paragraph on page 14, lines 10-13, as follows:

The peptides E-12-H (SEQ ID NO:5) and E-12-D (SEQ ID NO:6) were determined with reference to the nucleotide sequences of the gene for human profilaggrin which are described by GAN S.Q et al. [Biochemistry, 29: 9432-9440, (1990)].

Please amend the paragraph on page 14, lines 14-21, as follows:

The peptide of 14 amino acids E-12-H having the sequence (1-letter code):

NH2-EQSADSSRHSGSGH-COOH (SEQ ID NO:5)

comprises 1 arginine residue, and the peptide of 14 amino acids E-12-D having the sequence (1-letter code):

NH2-ESSRDGSRHPRSHD-COOH (SEQ ID NO:6)

comprises 3 arginine residues.

Please amend the paragraph on page 14, lines 27-29, as follows:

The citrullinated peptides E-12-H (SEQ ID NO:5) and E-12-D (SEQ ID NO:6) were directly synthesized by incorporation of a citrulline by replacing an arginine.

Please amend the paragraph on page 14, lines 30-33, as follows:

For the peptide E-12-D (SEQ ID NO:6), only the arginine residue corresponding to the 8^{th} amino acid of the sequence was replaced by a citrulline during peptide synthesis.

Please amend the paragraph on page 15, lines 4-25, as follows:

The wells of NUNC MAXISORP microtiter plates were respectively coated with the aid of the noncitrullinated and citrullinated peptides E-12-D (SEQ ID NO:6) and E-12-H (SEQ ID NO:5), diluted to a concentration of 5μg/ml in a PBS buffer (pH: 7.4) and incubated overnight at 4°C (final volume: 100 μg/well). The wells were saturated for 30 minutes at 37°C in PBS-Tween 20, 0.05%, 2.5% gelatin, 200 μl/well. The negative control serum (normal serum) was diluted 1/120. The antifilaggrin antibodies were diluted in PBS-Tween 20, 0.05% - 0.5% gelatin (PBS TG) such that the final anti-filaggrin autoantibody concentrations are those indicated in the

accompanying Table I. The negative control serum, the RA sera and the anti-filaggrin antibodies were added (final volume: 100 µl/well) and incubated for 1 hour at 37°C and overnight at 4°C. Peroxidase-labeled goat antibodies anti-gamma heavy chains of the human immunoglobulins (marketed by the company SOUTHERN BIOTECHNOLOGIES) were added to each well (dilution in PBSTG: 1/2000, final volume: 100 µl/well) and incubated for 1 hour at 37°C. The revealing was carried out by addition of orthophenylenediamine (2 mg/ml, for 10 minutes).

In The Claims:

3. (Amended) The artificial antigen as claimed in claim 2, which consists of a peptide comprising all or part of at least one sequence derived from SEQ ID NO:3 [the sequence corresponding to amino acids 71 to 119 of a human filaggrin unit], by replacing at least one arginine residue with a citrulline residue.

Application No.: 09/254,032

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Application needs to provide the corresponding SEQ ID NO. in the claims and specification.

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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